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EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	

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18

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/297,486	Applicant(s) MARTIN ET AL.	
	Examiner Richard Schnizer	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cov r sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,14,15 and 37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,14,15 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's amendment filed 6/4/02 was entered as Paper No. 17.

Claims 10-13, 16-36, and 38 were canceled as requested.

Claims 1-9, 14, 15, and 37 remain pending and are under consideration in this Office Action.

Claim Objections Withdrawn

Applicant's amendments overcame the standing objections to claims 1-9, 14, 15, and 37.

Claim Rejections Withdrawn

The rejections of claims 1-9 under 35 USC 102 are withdrawn in view of Applicant's amendment requiring periadventitial administration of the nucleic acid.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9, 14, 15, and 37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of treating intimal hyperplasia at a site of intimal thickening in a rabbit by administering to the site a DNA expression vector encoding an

agonist of Flt-1 and Flk-1/KDR receptors, and for methods of stimulating angiogenesis and inducing re-endothelialization, as known in the prior art, does not reasonably provide enablement for treatment of any other vascular disorder in any species other than a rabbit, and does not reasonably provide enablement for treatment of any vascular disorder in any species using any VEGF receptor agonist which is not an agonist for both Flt-1 and Flk-1/KDR receptors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims, for the reasons of record in Paper No. 15.

As a preliminary matter, it is noted that the claims do not require any specific outcome as a result of the method steps (see rejection under 35 USC 112, second paragraph, below). As noted below under 35 USC 102 rejections, the prior art teaches methods of stimulating angiogenesis and re-endothelialization which employ the method steps of the instant invention. Because these methods were well known in the art at the time of filing, the specification is considered to be enabling for them.

The claimed invention embraces methods of treatment or prevention of intimal hyperplasia (claims 1-9), and methods of therapy for a condition that can be treated or prevented by stimulation of NO or prostacyclin production. The recited method steps require administration of a nucleic acid encoding any agonist of any receptor to which VEGF binds. There is no limitation on the site to which the nucleic acid is delivered, or the identity or function

of the VEGF receptor (VEGFR). Only claim 8 limits the identity of the VEGFR agonist. Only claim 9 places any limitation on the mode by which the nucleic acid is delivered.

VEGF receptors and receptor agonists

The prior art teaches that there are at least three types of VEGF receptor: VEGFR-1 (Flt-1), VEGFR-2 (Flk-1/KDR), and VEGFR-3. See Joukov et al (J. Biol. Chem 273(12): 6599-6602, 3/1998), page 6599, column 2, lines 1-20. While these receptors bind several agonists, they do not all bind the same agonists. For example, VEGF binds both VEGFR-1 and VEGFR-2, while placental growth factor (PIGF) binds only VEGFR-1, and VEGF-C binds VEGFR-2 only. Furthermore, binding of these agonists results in different outcomes depending on the nature of the agonist and/or the location of the receptor. For example, Joukov et al teach that although both VEGF and VEGF-C bind VEGFR-2, VEGF promotes the growth of blood vessels, whereas VEGF-C promotes the growth of lymphatic vessels. See abstract, and page 6599, column 2, lines 15-19. Moreover, although PIGF is structurally similar to other members of the PDGF/VEGF family, and it binds to VEGF-1, its function *in vivo* was unknown at the time of filing. See Olofsson et al (Proc. Nat. Acad. Sci. USA 93: 2576-258, 3/1996) page 2576, last sentence of column 1. While the specification teaches that the function of the invention likely depends on binding VEGFR-1 and VEGFR-2 (see page 5, lines 14-19), no VEGFR agonist is excluded from the scope of claims 1-7, 9, 14, 15, and 37. However, the specification fails to teach how to use all VEGFR agonists in the invention, and in view of the fact that some VEGFR agonists have

activities which are markedly different from VEGF, or are unknown, there is reason to doubt that these agonists could be used in the invention as claimed.

Nucleic acid-mediated therapy and in vivo vector targeting

At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art. This is reflected by three recently published reviews. Orkin (Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy, 1995) teaches that "significant problems remain in all basic aspects of gene therapy. Major difficulties at the basic level include shortcomings in all current transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host" (page 1, item 3). Orkin teaches that problems exist in delivering nucleic acid sequences to the appropriate target cell or tissue and achieving the appropriate level of expression within that cell or tissue (page 9). Verma et al (Nature 389: 239-242, 1997) teach that "there is still no single outcome that we can point to as a success story (p. 239, col 1). The authors state further, "Thus far, the problem has been the inability to deliver genes efficiently and to obtain sustained expression" (p.239, col. 3). Anderson (Nature 392:25-30, 1998) confirms the unpredictable state of the art, stating that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease" (p. 25, col. 1) and concluding, "Several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered" (p.30).

Because the instant claims do not limit the mode of delivery of nucleic acids, the claims embrace systemic delivery of the therapeutic nucleic acid compositions. However, while progress has been made in recent years for *in vivo* gene transfer, vector targeting *in vivo* to desired sites continues to be unpredictable and inefficient. This is supported by numerous teachings available in the art. For example, Miller (1995) reviews the types of vectors available for *in vivo* gene therapy, including retroviral, adenoviral, liposomal, and molecular conjugates, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (1998) reviews ligand-targeted receptor mediated vectors, and indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise, but which are currently even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma et al. (1997) reviews various vectors known in the art for use in gene therapy and the problems which are associated with each. Verma (1997) clearly indicates that at the time of the claimed invention resolution to vector targeting had not been achieved in the art (see entire article). Verma discusses the role of the immune system in inhibiting the efficient targeting of viral vectors such that efficient expression is not achieved (see page 239 and 2nd and 3rd column

of page 242. Verma also indicates that appropriate enhancer-promoter sequences can improve expression, but that the "search for such [useful] combinations is a case of trial and error for a given cell type" (page 240, sentence bridging columns 2 and 3). Crystal (1995) also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409). While the specification supports efficient transfer for direct application of nucleic acids to the site of intimal thickening in a rabbit, the specification fails to teach one of skill in the art how to overcome the unpredictability for vector targeting such that efficient gene transfer is achieved by any other mode of delivery. The specification fails to teach any specific targeting techniques, fails to provide any working examples which encompass vector targeting, and fails to direct the skilled artisan to any teachings of targeting strategies known in the art which would allow one of skill in the art to practice the claimed invention without undue experimentation.

With specific respect to therapies based on the transfer of VEGF to the arterial wall, Laitinen (Pharm. Res. 47(4): 251-254, 4/1998) teaches that although promising effects on cardiovascular diseases have been noted by adventitial delivery of genes in animal models using the collar device disclosed at page 16, lines 21-23 of the specification, "further studies regarding gene transfer techniques, vectors, and safety of procedures are needed before a full therapeutic potential of gene therapy in vascular diseases can be evaluated." See abstract. See also sentence bridging pages 252 and 253, and last sentence of CONCLUSIONS on page 253. Thus the

treatment of vascular diseases in general by delivery of VEGF nucleic acids was unpredictable at the time the invention was filed.

Hypertension and diseases related to NO and prostacyclin production

The claims explicitly encompass methods of treating hypertension, and in particular, essential hypertension, pulmonary hypertension, and cor pulmonale. Robbins (In Pathologic basis of Disease, 5th Edition, W.B. Saunders Company, Publishers, 1994) teaches that essential hypertension is caused by a primary increase in cardiac output due to reduced renal sodium excretion, or by vasoconstrictive influences including behavioral factors, increased release of vasoconstrictors such as angiotensin II or catecholamines, or an increased sensitivity of vascular smooth leading to increased contraction. See page 485, column 1, first sentence of first full paragraph; page 487, column 1, line 5 to column 2, line 6. Although the specification teaches how to inhibit intimal proliferation in a rabbit model, intimal proliferation does not appear to be recognized in the art as a cause of essential hypertension. Furthermore the specification fails to teach how to use the instant invention to increase renal sodium excretion, affect behavioral factors responsible for hypertension, decrease the release of vasoconstrictors, or an decrease the sensitivity of vascular smooth leading to increased contraction. The specification indicates at page 6, lines 4-10 that NO levels are low in individuals suffering from hypertension, and concludes that VEGF may be useful in treating hypertension because it causes an increase in NO. However, no cause and effect relationship between NO levels and hypertension is established in the specification or the prior art of record. Thus it is no more likely that low NO levels cause

hypertension than it is that low NO levels are caused by hypertension, thus there is insufficient evidence to indicate that increasing NO levels would reduce any type of hypertension. Even if increasing NO levels did decrease hypertension, the specification has failed to teach how much of any VEGFR agonist is required to produce sufficient NO for this effect, how to produce the appropriate amount of the agonist *in vivo,* or where to produce it. The specification also fails to identify a single disease which is related to prostacyclin production, fails to teach how much VEGF agonist should be expressed in order to stimulate prostacyclin production, how much prostacyclin production is required to treat any disease, where it should be produced, or how to obtain the appropriate amount of VEGF expression. Moreover, Yla-Herttuala and Martin, co-inventors in the instant Application, indicated in a paper published 1/15/00 that the design of strategies in which VEGF genes are delivered for the purpose of stimulating therapeutic levels of NO and prostacyclins might be possible in the future. See page 217, paragraph bridging columns 1 and 2. In light of this statement, and the state of the art as established by Orkin, Verma, and Anderson above, one must conclude that the practice of stimulating therapeutic NO and prostacyclin production by VEGF nucleic acid administration was not routine and was highly unpredictable at the time of the invention. Yla-Herttuala and Martin also stress the need for further developments in gene-transfer vector and, gene delivery techniques before the therapeutic potential of gene therapy in cardiovascular disease can be assessed. See abstract. In view of the state of the art of gene therapy at the time of the invention, and after time of the invention as acknowledged by the inventors, and the failure of the specification to provide sufficient teaching

or examples, one of skill in the art would have to perform undue experimentation to treat hypertension, or to stimulate therapeutic NO or prostacyclin production, using the methods of the instant invention.

Relevance of animal models of intimal hyperplasia to human disease and treatment

The prior art teaches that successful treatment of intimal hyperplasia in small animal models is not predictive of success in other animals, particularly in humans. Muller et al (J. Amer. Coll. Cardiol. 19(2):418-432, 1992) teach that, as of 1992, greater than 50 studies had shown that at least 9 different classes of pharmacological agents inhibit intimal proliferation in response to arterial injury in animal models. However, none of these agents reproducibly reduced the incidence of restenosis after coronary balloon angioplasty in humans. To explain these results, Muller considered the differences between the various systems. Significant interspecies and intraspecies differences were found to exist among the various animal models, particularly with respect to the extent and composition of neointimal thickening, drug and lipid metabolism, and the activity of coagulation and fibrinolytic systems. The instant specification teaches a single example of a therapeutic result in a rabbit model of intimal hyperplasia by delivery of a liposomal composition comprising plasmid DNA encoding VEGF to the precise site of intimal thickening. See Example 1, pages 33-38. With respect to rabbit models, Muller notes that rabbit arteries are not necessarily structurally equivalent to human arteries. For example, the amount of elastin in the media of coronary arteries is less than that in larger mammals, the intima is thinner, and the subendothelial space between the endothelium and the internal elastic lamina

is very narrow and virtually acellular. A similar intimal structure is found in the arteries of humans only during fetal and early neonatal life. See paragraph bridging columns 1 and 2 on page 420. Muller teaches that these differences may account for the variability in sensitivity of various animal models to treatments, and should be considered carefully in the interpretation of experimental studies. See abstract. Lafont et al (Ann. Card. Ang. 44(7): 349-353, 9/1995), review the results of fifteen years of research prior to 1995, and conclude that "[a]ll the restenosis strategies based on inhibition of smooth muscle cell proliferation, which successfully limited restenosis in animal models have failed in man, due to hazardous extrapolations from experimental models which are very different from the atheromatous lesions observed in man". See abstract. Lafont et al (Card. Res. 39(1): 50-59, 7/1998) further indicates that while animal models may be useful for determining the mechanism of a drug on smooth muscle cell proliferation, positive results should not be interpreted to mean that a given treatment will function in humans. "The extrapolation of animal studies directly to man is unreasonable given the vast differences between animal models and man, and the complexity of the restenotic process." See page 54, column 2, lines 3-12. The same concerns would apply to the treatment of hypertension and stenosis, due to the differences in physiology among the various models. In fact, the unpredictability in extrapolating results of such studies to humans was noted as late as 1999, when Johnson et al taught that small animal models "lacked efficacy in predicting the success of interventions to inhibit restenosis in humans", and found that small animal models fail to closely simulate human atherosclerosis and stenotic lesions. See abstract. For these reasons,

even if the specification provided adequate guidance to one of skill in the art to practice the full scope of the invention in rabbits, which it does not, the enabled use of the claimed invention would be limited to the treatment of rabbits.

In summary, at the time of the invention, those of skill in the art recognized that one could not accurately extrapolate positive results from rat models of smooth muscle cell proliferation to other animals, particularly humans; the specification fails to improve on this situation by providing guidance which would allow such extrapolation; the specification fails to provide any working example of treatment in any organism other than a rabbit, or of any disorder other than intimal hyperplasia; the specification fails to teach how to perform the claimed methods by delivering nucleic acids to any site other than a site of intimal thickening, or with any VEGFR agonist other than those which bind and agonize both Flt-1 and Flk-1/KDR receptors. For these reasons, one of skill in the art could not practice the claimed methods commensurate in scope with the claims without undue experimentation.

Response to Arguments

Applicant's arguments and the Declaration of Dr. Martin, filed 6/3/02 have been fully considered but they are not persuasive.

At page 3 paragraph 5 of the response, Applicant asserts that "the claims are enabled for all VEGF receptors and receptor agonists are known in the art". This assertion is unpersuasive because it is unsupported by evidence or reasoning.

In the paragraph bridging pages 3 and 4 of the response, Applicant asserts that the invention is enabled for deliver and expression of a nucleic acid in a target cell, noting that claim 1 has been amended to require administration of the nucleic acid to the blood vessel being treated. It is noted that this amendment does not affect claims 14, 15, and 37 which continue to read on treatment by administration to any site, systemically or locally. Applicant relies for support on the Declaration of Dr. Martin, noting that it is unsigned. Because the Declaration is unsigned it constitutes hearsay evidence only, and is unpersuasive. However, even if the Declaration were signed it would not support the invention as claimed. The Declaration presents the results of an experiment in which nucleic acids encoding VEGF-D were delivered **to the site of surgery** in pigs which had undergone surgical anastomosis of the carotid artery and internal jugular vein. As discussed in the specification at page 1, lines 18-23, surgical treatments like this and angioplasty can give rise to intimal hyperplasia at the site of surgery or balloon-induced damage. For this reason, any significant results of the experiment could support only methods in which the nucleic acid was delivered **to the site of damage**. In contrast, the claims as amended require only that the nucleic acid must be delivered to the blood vessel, and fail to require delivery to the site of intimal hyperplasia in that blood vessel. As applicant clearly understands, the carotid artery on which the experiments were performed is several inches long. There is no reason to expect that nucleic acids delivered to cells several inches from the site of injury on the same vessel will have any effect on the cells in the injured area, yet the claims continue to embrace that as an embodiment of the invention. The specification suggests that therapeutic

effect of the method owes to production of NO or prostacyclins. However, the specification fails to teach how much of any VEGFR agonist is required to produce sufficient NO or prostacyclin for any effect, how to produce the appropriate amount of the agonist *in vivo,* or how to deliver appropriate amounts of NO or prostacyclin from transfected cells to target cells that are not located **at the site** of transfection. Furthermore the significance of the results presented in the Declaration is unclear for several reasons. There is no statistical analysis, the sample size is small, and the results seem to indicate that the treatment may in fact increase intimal hyperplasia over time. See in particular, page 5, first sentence of paragraph 4 which indicates that at day 60 there was an increased degree of intimal proliferation/fibrosis and a reduction in luminal diameter in the groups which received VEGF-D adenovirus, when compared with the controls, and that luminal occlusion occurred only in animals treated with VEGF-D. Finally, because intimal hyperplasia is known to occur in about 30% of arterial bypasses after two years (see specification at page 2, lines 10 and 11), it is not clear that an inhibition of intimal proliferation in 50% of individuals at 28 days after surgery is significant at all, particularly in view of the small sample size and the fact that after 60 days intimal proliferation and luminal occlusion increased in VEGF-treated individuals.

At paragraph 1 of page 4, Applicant asserts that the Examiner failed to provide specific evidence that the claimed invention would not function to treat hypertension and other diseases associated with NO and prostacyclin production. Applicant relies for support on the findings of the court in In re Marzocchi in which the court held that Applicant's statements must be held as

true unless the Patent Office can recite specific reasons to doubt the validity of those statements. Applicant's attention is directed to the rejection which states that "even if increasing NO levels did decrease hypertension, the specification has failed to teach how much of any VEGFR agonist is required to produce sufficient NO for this effect, how to produce the appropriate amount of the agonist *in vivo,* or where to produce it. The specification also fails to identify a single disease which is related to prostacyclin production, fails to teach how much VEGF agonist should be expressed in order to stimulate prostacyclin production, how much prostacyclin production is required to treat any disease, where it should be produced, or how to obtain the appropriate amount of VEGF expression." Applicant has failed to respond to this portion of the rejection.

In the final paragraph of page 4, Applicant addresses the significance of the Muller reference by arguing that the instant invention is unrelated to reducing the incidence of restenosis after balloon angioplasty, noting that balloon angioplasty destroys the epithelium whereas the instant invention involves treatment of intimal hyperplasia where the endothelium is wholly or largely intact. This argument is unpersuasive because it lacks support. Muller and Lafont indicate that restenosis after angioplasty is caused by intimal hyperplasia, and that methods and reagents for reducing intimal hyperplasia in small animals have without exception failed to prevent restenosis in humans. It follows therefore that these methods and reagents failed to inhibit intimal hyperplasia in humans. Applicant has failed to show why inhibition of intimal hyperplasia in blood vessels containing damaged epithelia is any different than intimal hyperplasia in blood vessels with intact epithelia. For this reason, the argument is unpersuasive.

It is noted that the specification seems to indicate that intimal hyperplasia in damaged epithelia is similar to intimal hyperplasia in undamaged epithelia. See page 1, lines 18-27 which indicates that intimal proliferation occurs and causes restenosis in response to both anastomosis and balloon angioplasty procedures. In view of the fact that the Declaration of Dr. Martin dealt with an anastomosis procedure, the Examiner concludes that Applicant considers anastomosis to result in vessels with largely intact epithelia.

In the first paragraph of page 5 Applicant argues that the scope of enablement is not limited to rabbits, relying for support on the declaration of Dr. Martin. This argument is unpersuasive because, as noted above, the declaration is unsigned and is only here say evidence, and in any case the results presented do not appear to be significant due to a lack of statistical analysis, small sample size, and the apparent result that VEGF treatment increased intimal proliferation and occlusion after 60 days relative to controls.

For these reasons, the rejection is maintained.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9, 14, 15, and 37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-9, 14, 15, and 37 are indefinite because the method steps are not concordant with the purpose set forth in the preamble. The claims recite no step in which treatment is effected, and the claims do not require any specific outcome as a result of the method steps.

Applicant has not responded to this ground of rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 14, 15 and 37 stand rejected under 35 U.S.C. 102(e) as being anticipated by either of two US Patents issued to Isner (Nos. 6,121,246, or 6,258,787) for the reasons of record in Paper No. 17.

6,121,246 teaches a method of inducing formation of new blood vessels by injecting into a human host an effective amount of a DNA sequence encoding vascular endothelial growth factor. See claim 2 at column 13. The nucleic acid may be in a viral or liposomal vector. See column 5, lines 51-53. The DNA may also encode active fragments of VEGF such as VEGF-165. See column 6, lines 61-66 and column 7, lines 7-12. The instant specification teaches that

VEGF-165 is equivalent to SEQ ID NO:4 of instant claim 8. Although 6,121,246 is silent as to treatment of the disorders recited in the instant claims, the claims of 6,121,246 recite the same method steps as the instant claims and can be considered to have the same results. It is noted that none of the instant claims recites any result associated with the method steps, for this reason an anticipation rejection is appropriate.

Thus 6,121,246 anticipates the claims.

6,258,787 teaches a method for inducing re-endothelialization in a blood vessel by administration of a nucleic acid encoding VEGF, wherein the blood vessel comprises a portion which is denuded of its epithelial lining. See claim 2 at column 19. The nucleic acid may be delivered in a liposomal or a viral vector. See column 6, lines 11-18. The nucleic acid may encode active fragments of VEGF such as VEGF-165. See column 9, lines 39-55. The instant specification teaches that VEGF-165 is equivalent to SEQ ID NO:4 of instant claim 8. The specification teaches that the blood vessel may be partially denuded of its endothelium by use of an arterial balloon catheter. See e.g. column 2, lines 20-27. Because denudation would only occur at the site of expansion of the balloon, the endothelium of the rest of the blood vessel should remain largely intact. Although 6,258,787 is silent as to treatment of the disorders recited in the instant claims, the claims of 6,258,787 recite the same method steps as the instant claims and can be considered to have the same results. It is noted that none of the instant claims recites any result associated with the method steps, for this reason an anticipation rejection is appropriate.

Thus 6,258,787 anticipates the claims.

Claims 14, 15, and 37 are rejected under 35 U.S.C. 102(a) as being anticipated by either one of Isner et al (LANCET 348:370-374, 8/1996) or Takeshita et al (Biochem. Biophys. Res. Comm. 227:628-635 10/14/96) for the reasons of record in Paper No. 17.

Isner teaches a method of inducing formation of new blood vessels by injecting into a human host an effective amount of a DNA sequence encoding VEGF-165. The nucleic acid was delivered in a hydrogel polymer vector. See abstract and paragraph bridging columns 1 and 2 on page 370. The instant specification teaches that VEGF-165 is equivalent to SEQ ID NO:4 of instant claim 8. Although Isner is silent as to treatment of the disorders recited in the instant claims, Isner recites the same method steps as the instant claims and can be considered to have the same results. It is noted that none of the instant claims recites any result associated with the method steps, for this reason an anticipation rejection is appropriate.

Thus Isner anticipates the claims.

Takeshita teaches a method of inducing formation of new blood vessels by injecting into a human host an effective amount of a DNA sequence encoding VEGF-165. The nucleic acid was delivered in a hydrogel polymer vector. See abstract, and page 629, lines 4-7 of second paragraph. The instant specification teaches that VEGF-165 is equivalent to SEQ ID NO:4 of instant claim 8. Although Isner is silent as to treatment of the disorders recited in the instant claims, Isner recites the same method steps as the instant claims and can be considered to have

the same results. It is noted that none of the instant claims recites any result associated with the method steps, for this reason an anticipation rejection is appropriate.

Thus Takeshita anticipates the claims.

Response to Arguments

Applicant's arguments filed 6/3/02 have been fully considered but they are not persuasive.

At paragraphs 2 and 3 of page 6, Applicant argues that one of skill in the art would not have appreciated that the prior art methods might have any beneficial effect on non-denuded vessels., and that the cited art does not teach treatment following reendothelialization. This is unpersuasive because the claims do not require any effect on any vessel, denuded or otherwise, nor do they recite treatment following reendothelialization. Rather the claims are broadly drawn to treatment of any condition that can be treated or prevented by stimulation of NO or prostacyclins or both.

In paragraph 4 of page 6 Applicant notes that references that fail to teach every element of the claimed invention cannot anticipate the invention. This is unpersuasive becasue Applicant has failed to point out which claim limitations are not taught.

In paragraph 1 of page 7, Applicant asserts that the prior art fails to teach methods where the endothelium of the blood vessel is wholly or largely intact. This is unpersuasive because the rejected claims make no such requirement.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader, can be reached at 703-308-0447. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014. Additionally correspondence can be transmitted to

the following RIGHTFAX numbers: 703-872-9306 for correspondence before final rejection, and 703-872-9307 for correspondence after final rejection.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

Richard Schnizer, Ph.D.

JAMES KETTER
PRIMARY EXAMINER